Pneumococcal Vaccines for Older Adults: What is the right approach?

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Senior Subject Matter Expert, IHRC Inc.

My background and funding

- US Centers for Disease Control and Prevention (CDC), retired July 1

- Current funding:
  - IHRC, Inc.: consultant for CDC
  - Limited-time consulting: Guidepoint, SutroVax, Inc

Pneumococcal vaccines for older adults
What is the right approach?

- Background -- why the need for vaccines for adults
- Considerations and reconsiderations for using conjugate vaccine-- the US experience
- What do we want from a pneumococcal vaccine for adults?

Colonization, Mucosal Disease, Invasive Disease

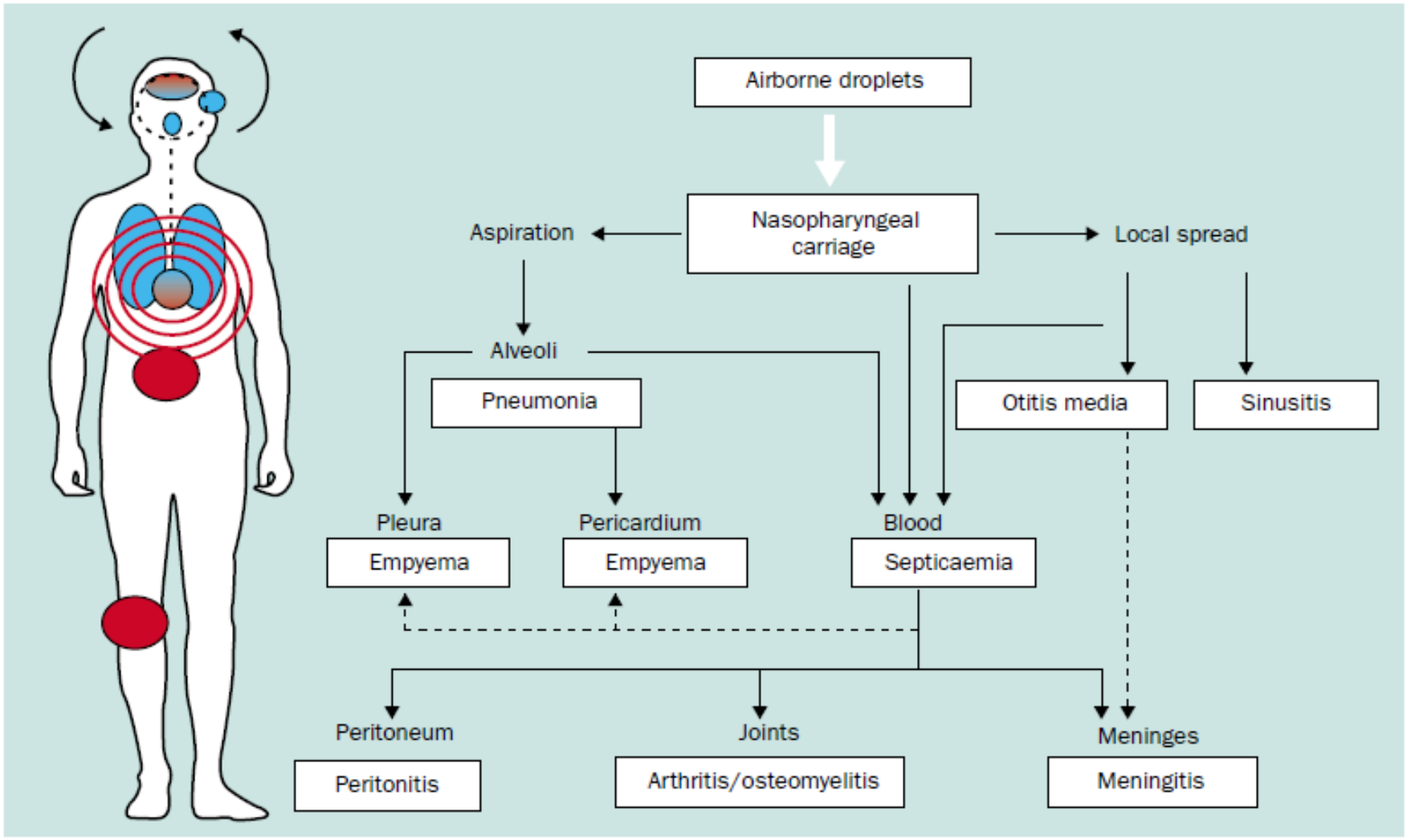

Figure 1. Pathogenic route for S pneumoniae infection. Redrawn from reference 2. Organs infected through the airborne and haematogenic routes are depicted in blue and red, respectively.

Bogaert, Lancet Infect Dis 2004;4:144-54

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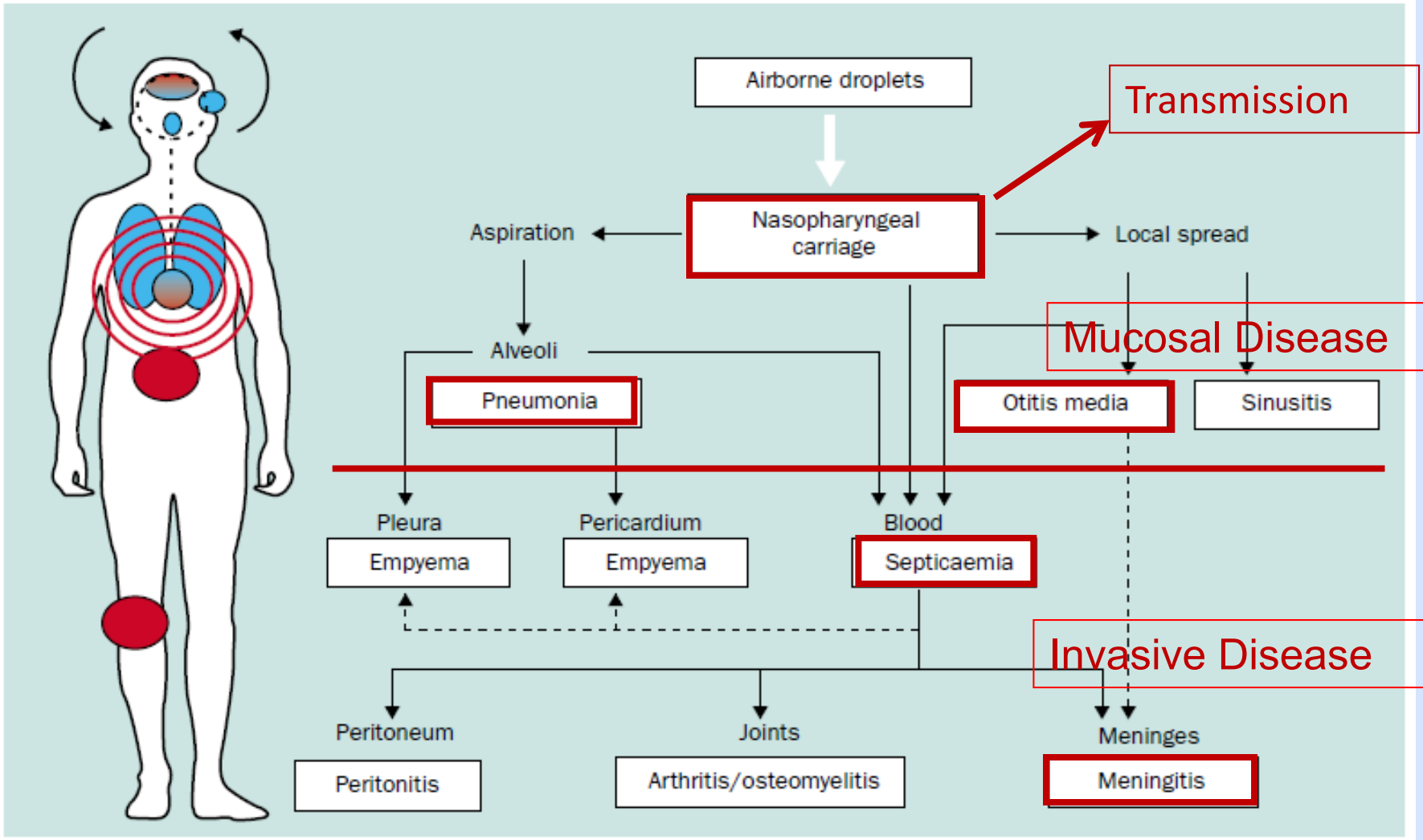

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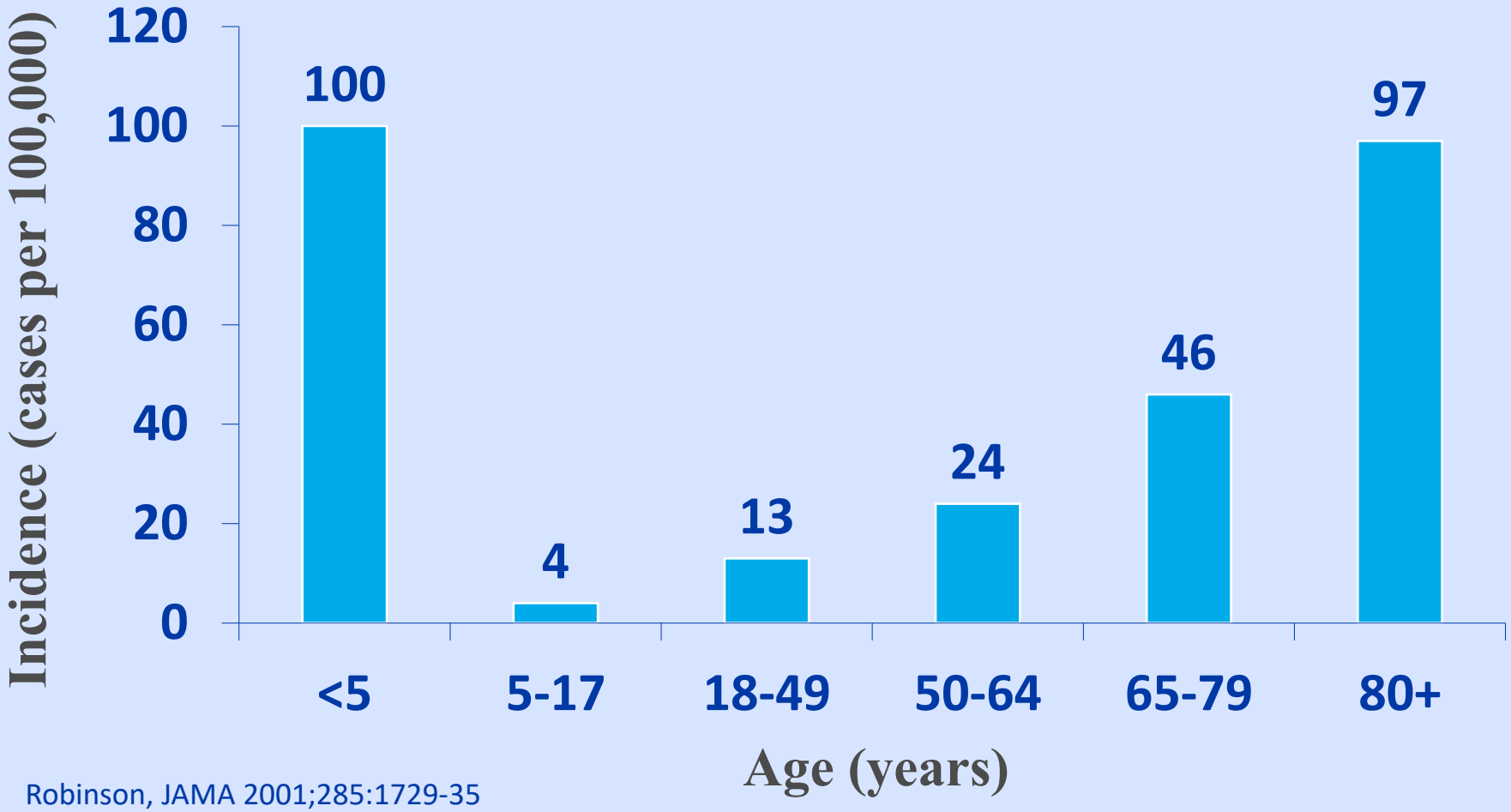
Age-Specific Incidence of Invasive Pneumococcal Disease, US, 1998



Robinson, JAMA 2001;285:1729-35

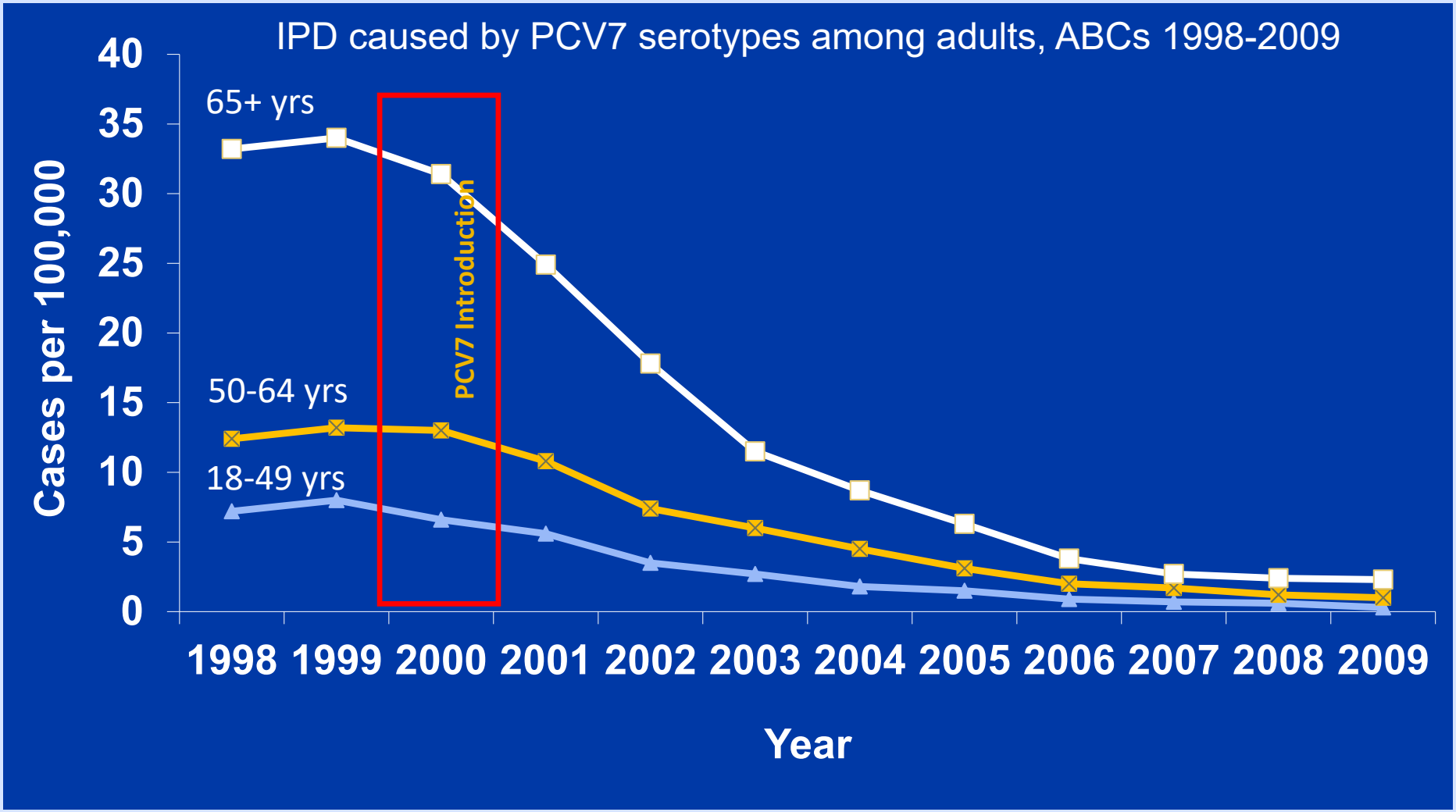

I've been calling you all day.
That's a calculator.
Madly Odd!

Vaccines to Preserve Health

- People age 65+ years a large and growing segment of the population
- Many are heathy, active, engaged
- Immunizations a simple way to preserve health

Photo source: dailymail.co.uk from Reddit

Vaccinating children highly effective for preventing disease in adults



Moore, IDSA, 2009

Need better prevention measures for pneumonia in older adults

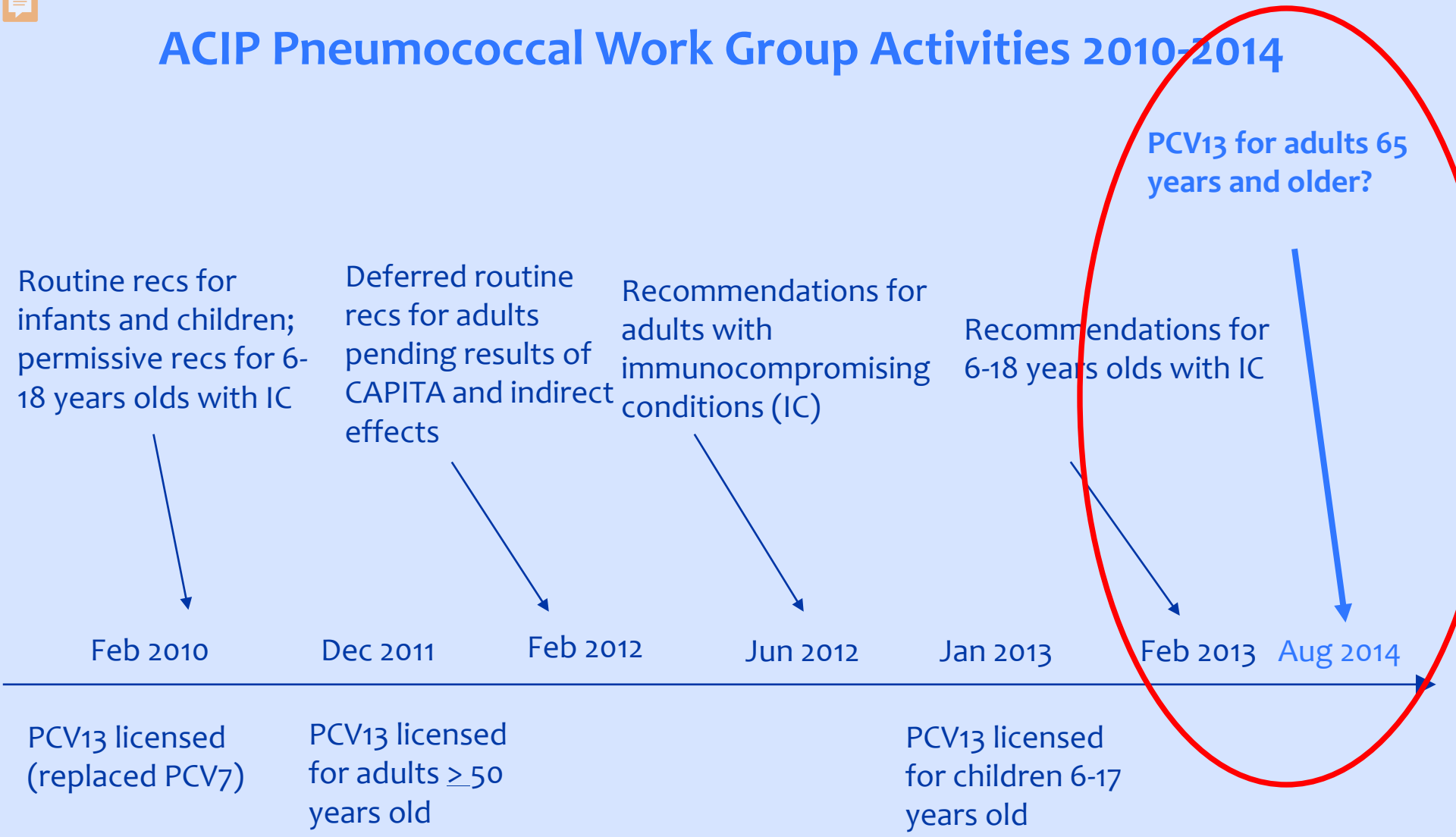
- Prevention measures targeting respiratory infections
  - Indirect effects from pediatric PCV program
  - 23-valent pneumococcal polysaccharide vaccine (PPSV23) used in US since 1983
  - Expanded flu vaccine recommendations and improved coverage
  - Smoking cessation and prevention program; second-hand smoke restricted in public areas

- In spite of these measures:
  - Pneumonia/influenza still 8th leading cause of death in US
  - >57,000 deaths in 2015 CDC.gov

Polysaccharide & Conjugate Vaccines: A Comparison

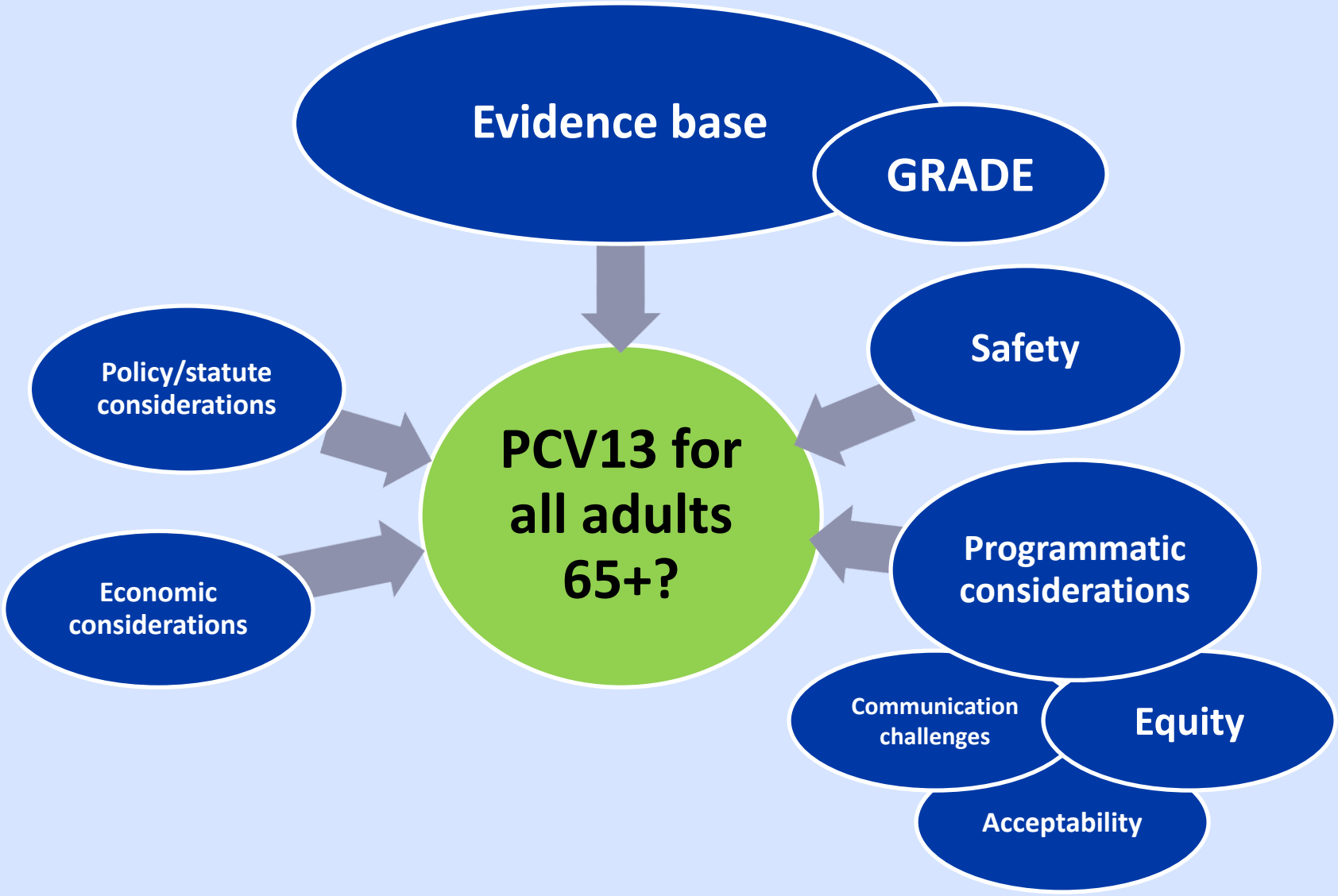
Characteristic	Polysaccharide	Conjugate
Components	Purified polysaccharide	Purified polysaccharide covalently bound to carrier protein
Immunogenic?	Only among >2 year-olds	All ages (T-dependant pathway)
First year available	1918→1977→1983	2000→2009→2010
Number of serotypes	4→14→23	7→10→13
Effect against bacteremia	Substantial	Substantial
Effect against carriage	None	Substantial
Effect against non-bacteremic pneumonia	No consensus	Moderate
Schedule	≤3 doses after age 2 years	4 doses <age 2 years; possibly 1 after
Cost	US $55	US $124
Examples	23-valent Pneumococcal Polysaccharide Vaccine (PPSV23)	13-Valent Pneumococcal Conjugate Vaccines (PCV13)

ACIP Pneumococcal Work Group Activities 2010-2014



IC = with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants

Considerations for changing vaccine policy



Community-acquired Pneumonia Immunization Trial in Adults

Netherlands The Journal of Medicine

ORIGINAL ARTICLE

Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults

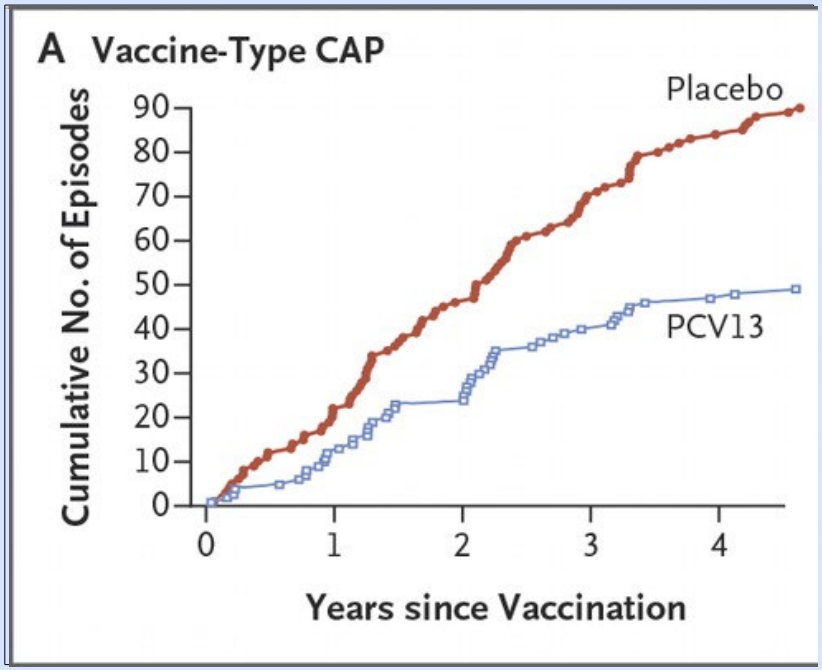
E. Hak[1,2*], D.E. Grobbee[1], E.A.M. Sanders[2], T.J.M. Verheij[1], M. Bolkenbaas[1], S.M. Huijts[1], W.C. Gruber[3], S. Tansey[3], A. McDonough[3], B. Thoma[3], S. Patterson[3], A.J. van Alphen[4], M.J.M. Bonten[1,5]

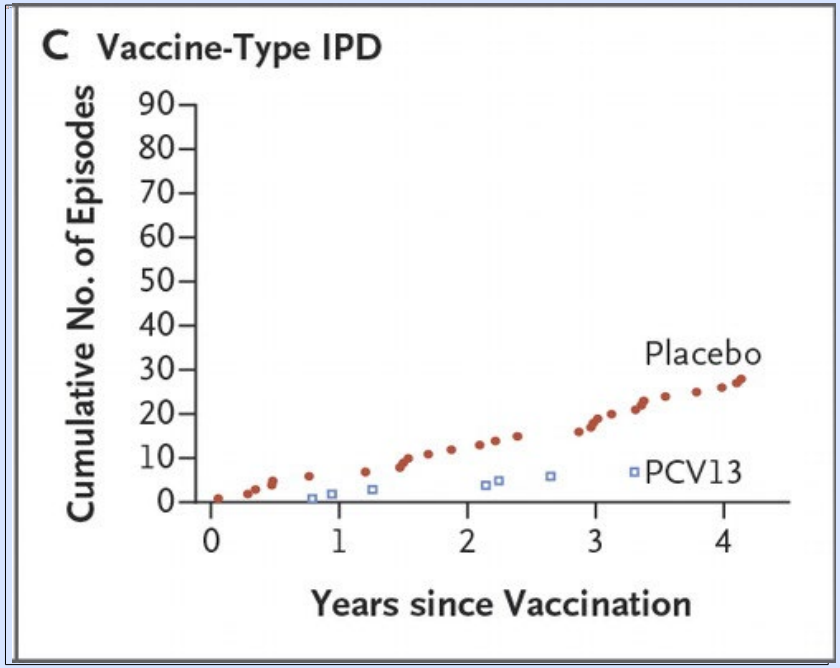
[1]Julius Center for Health Sciences and Primary Care, Departments of [2]Pediatric Immunology and Infectious Diseases, and [5]Medical Microbiology, University Medical Center Utrecht, the Netherlands, [3]Wyeth Vaccines Research, Wyeth, Pearl River New York, USA, [4]Netherlands Vaccine Institute, Bilthoven, the Netherlands, *corresponding author: tel.: +31 (0)88-756 82 14, fax: +31 (0)88-76 80 99, e-mail: e.hak@umcutrecht.nl

- Randomized, placebo-controlled trial of 84,496 adults ≥65yrs of age in the Netherlands
- Primary endpoint
  - Vaccine-type community-acquired pneumonia
  - Measured using serotype-specific urine antigen assay

Neth J Med 2008;66:378-83

CAPiTA: Cumulative Episodes of Efficacy End Points in the Per-Protocol Population





CAP vaccine efficacy 46% (22%, 63%)

IPD vaccine efficacy 75% (41%, 91%)

Bonten MJ et al. N Engl J Med 2015;372:1114-1125.

PCV in Older Adults: Quality of evidence (GRADE)

Comparison	Outcome	Study Design (# studies)	Findings	Quality of evidence	Overall evidence type
PCV13 vs. no vaccination	IPD	RCT (1)	Decreased risk among vaccinated	2	
PCV13 vs. no vaccination	Pneumonia	RCT (1)	Decreased risk among vaccinated	1	2
PCV7 or PCV13 vs. PPSV23	Immunogenicity	RCT (6)	Response improved for PCV vs. PPSV23 or no difference	2	
PCV13 vs. PPSV23	Serious and systemic adverse events	RCT (3)	No difference or decreased risk with PCV13	1	

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PCV13 no vacc					2
PCV7 o vs. PPSV23			difference		
PCV13 vs. PPSV23	Serious and systemic adverse events	RCT (3)	No difference or decreased risk with PCV13	1	

HIGH QUALITY EVIDENCE (I.e., this vaccine works)

OK, the vaccine works…

…but do we need it?

"We don't need PCV13 because vaccinating children has taken care of virtually all the disease."

Q: Disease rates have gone down…but have they gone down so far that vaccinating adults is pointless?

A: Need to do the math!

Modeling expected public health impact and cost-effectiveness of PCV13 for older adults in the U.S.

- Various strategies considered:
  - Vaccination at ages 50, 60, and 65 years
  - PCV13 instead of PPSV23
  - PCV13 in sequence with PPSV23

- Took into account:
  - Anticipated reductions in vaccine-serotype disease over time because of pediatric program (used PCV7 experience)
  - A guess at how quickly coverage would increase
  - Waning immunity over time after vaccination
  - Disease occurring only in nonimmunosuppressed persons
  - A lot of other stuff

Stoecker C et al. ACIP 2014 and J Gen Intern Med. 2016 Aug; 31(8): 901–908.

Expected public health impact and cost-effectiveness in the U.S.

- Adding PCV13 at age 65 years to existing PPSV23 recommendations likely the optimal strategy
  - PPSV23's extended serotype range helps with IPD; PCV13 helps with pneumonia
- Health benefits for cohort of 65-yo's vaccinated
  - 5000 fewer pneumonia hospitalizations
  - 7300 fewer outpatient pneumonias
- Cost-effectiveness comparable to other accepted adult interventions (base case: $62,000/QALY)
- But, cost-effectiveness likely to decrease over time
  - For 2019 cohort, $273,000/QALY

Stoecker C et al. ACIP 2014 and J Gen Intern Med. 2016 Aug; 31(8): 901–908.

Expected public health impact and cost-effectiveness in the U.S.

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Math supported giving PCV

3 helps with pneumonia

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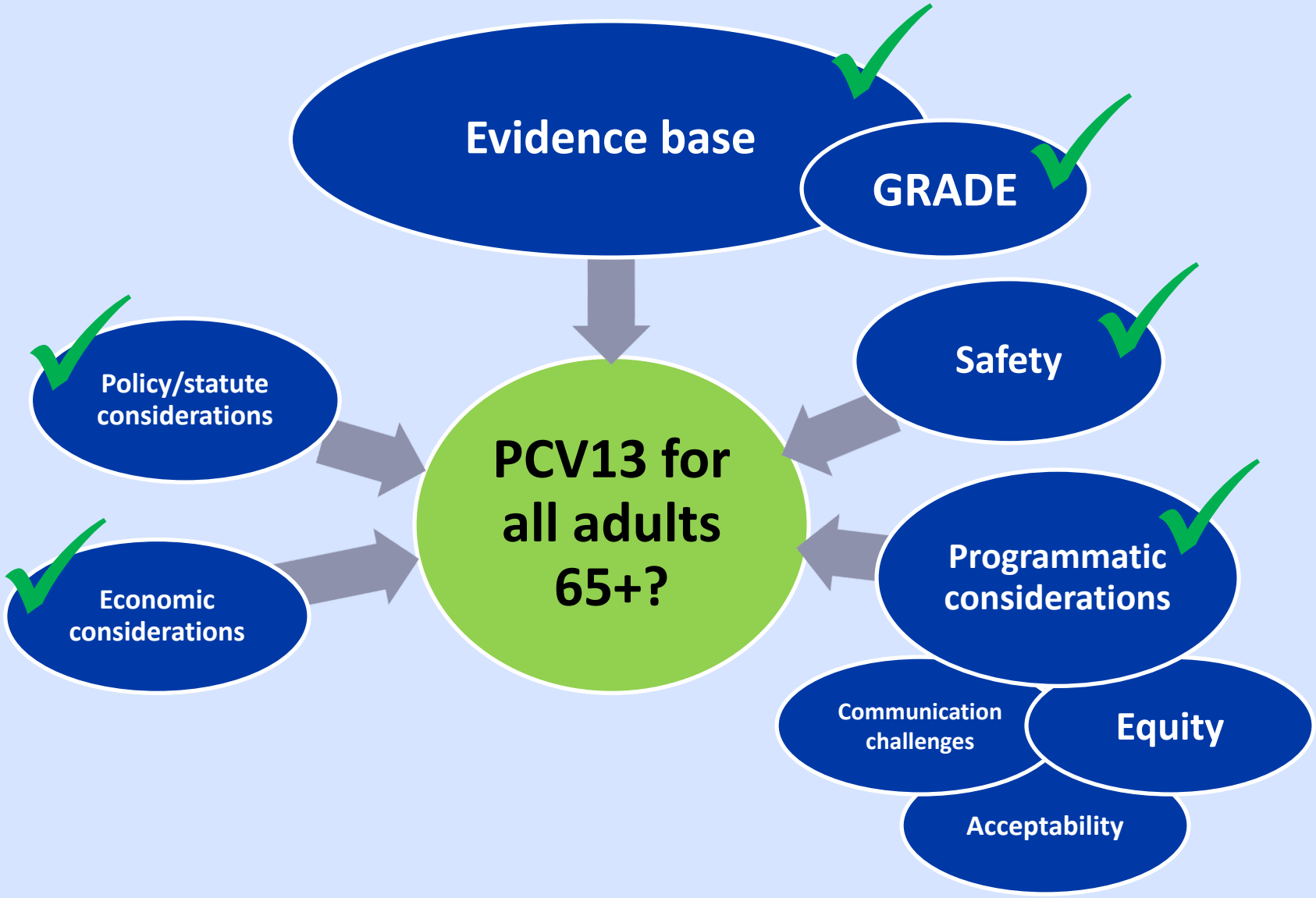
Caveats:

- **Need for PCV likely to drop over time**
- **US situation may not be applicable elsewhere**

Stoecker C et al. ACIP 2014 and J Gen Intern Med. 2016 Aug; 31(8): 901–908.

Considerations for changing vaccine policy



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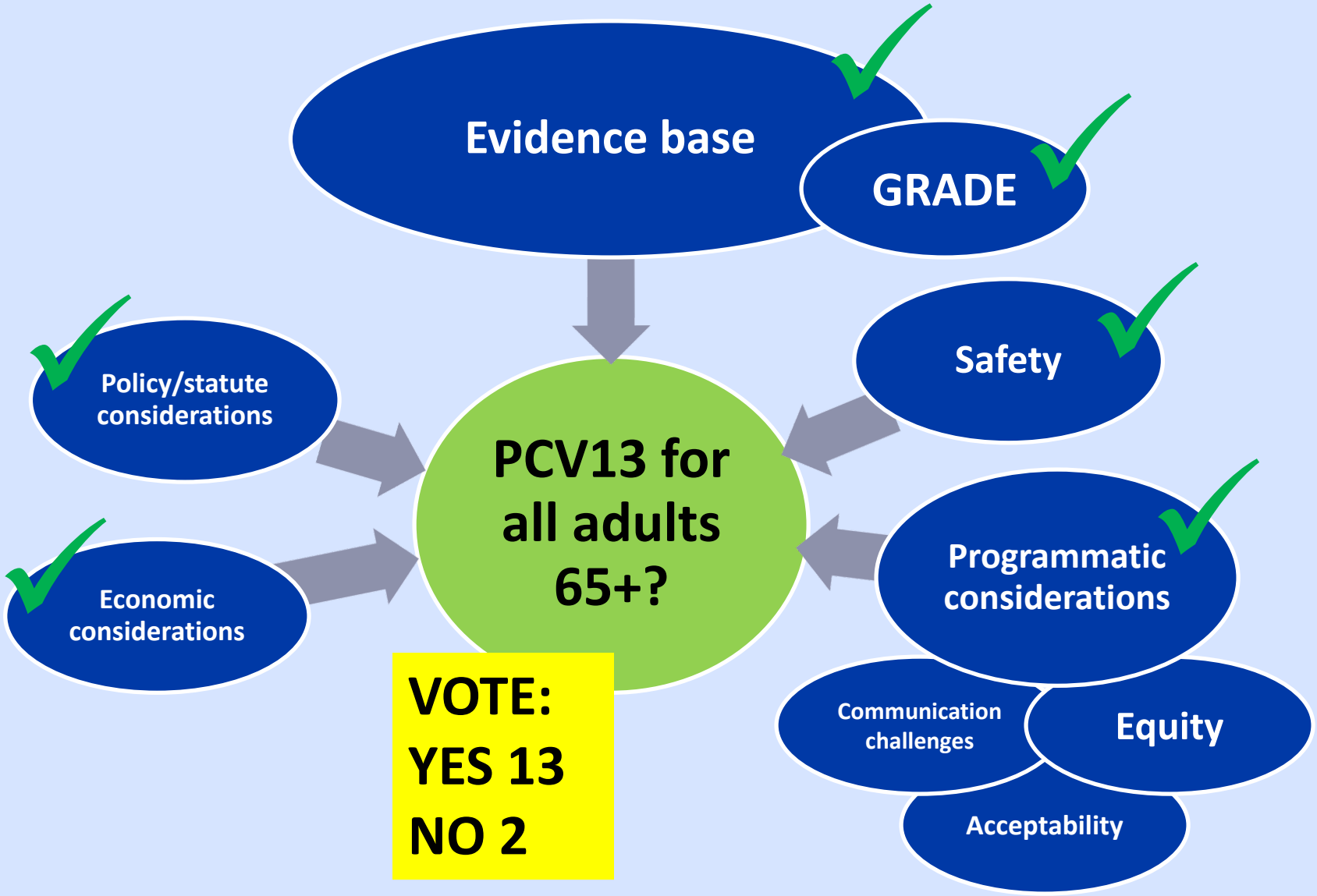


Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 63 / No. 37
September 19, 2014

- **2014 Advisory Committee on Immunization Practices (ACIP)**
  - Both PCV13 and PPSV23 should be routinely administered in series to all adults aged ≥65 years.
  - When possible, PCV13 given first followed by PPSV23 later
  - The recommendations for routine PCV13 use among adults aged ≥65 years will be reevaluated in 2018 and revised as needed.
- **2015 update:** interval between PCV13 and PPSV doses should be ≥ 1 year (regardless of order)

Tomczyk S et al. MMWR September 19, 2014 / 63(37);822-825
Kobayashi M et al. MMWR **September 4, 2015 / 64(34);944-947**

2018 ACIP Pneumococcal Vaccine Work Group

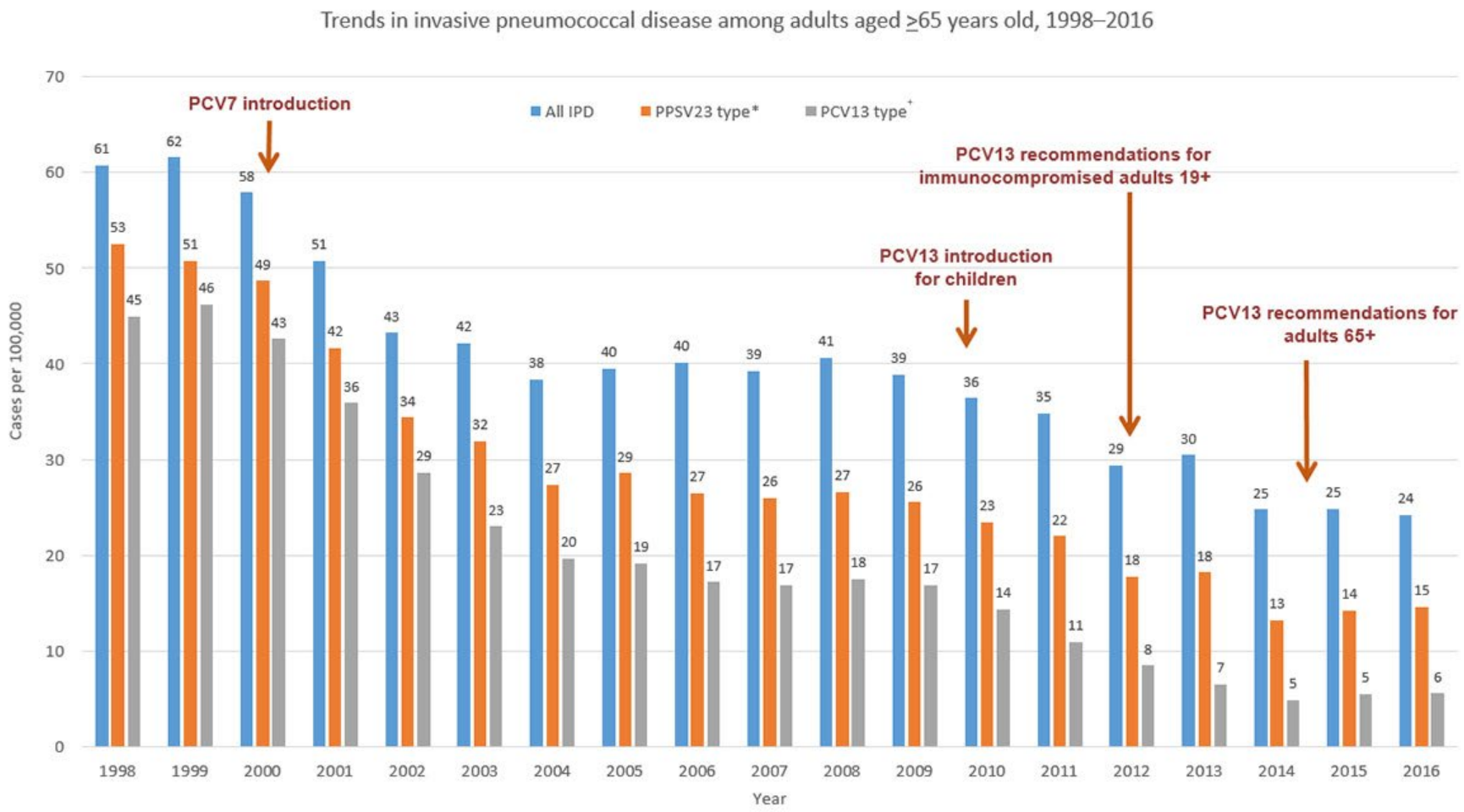
Mandate to:

- Review current data on efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines
- Assess recommendations considering up-to-date evidence and evidence strength
- Revise or update recommendations for pneumococcal vaccine use, as needed

Setting:

- PCV13 coverage modest
  - Increased to ~40% through 2017 among adults 65+ yrs
  - Lower among those 19-64 yrs with vaccine indications
- Safety assessment good
  - VAERS: mostly injection site reactions, no unexpected reports or patterns
  - VSDL: no increased risk of reactions compared to PPSV23

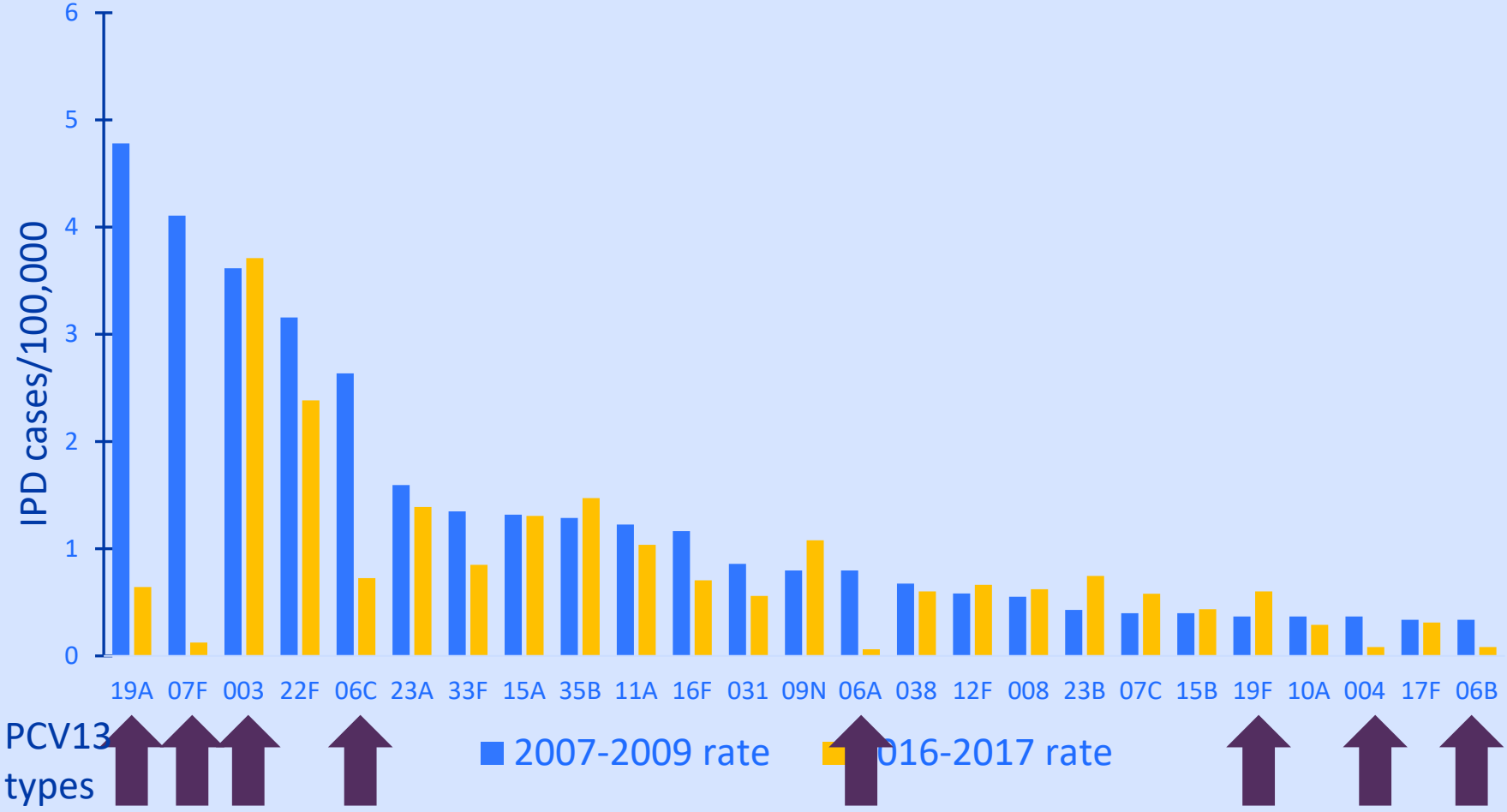
Invasive pneumococcal disease trends, adults 65+ Active Bacterial Core surveillance (ABCs)



*PPSV23 serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F

+PCV13 serotype: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Top serotypes causing IPD in US adults 65+, 2007-2009 and 2016-2017



Source: US Centers for Disease Control and Prevention, Active Bacterial Core surveillance

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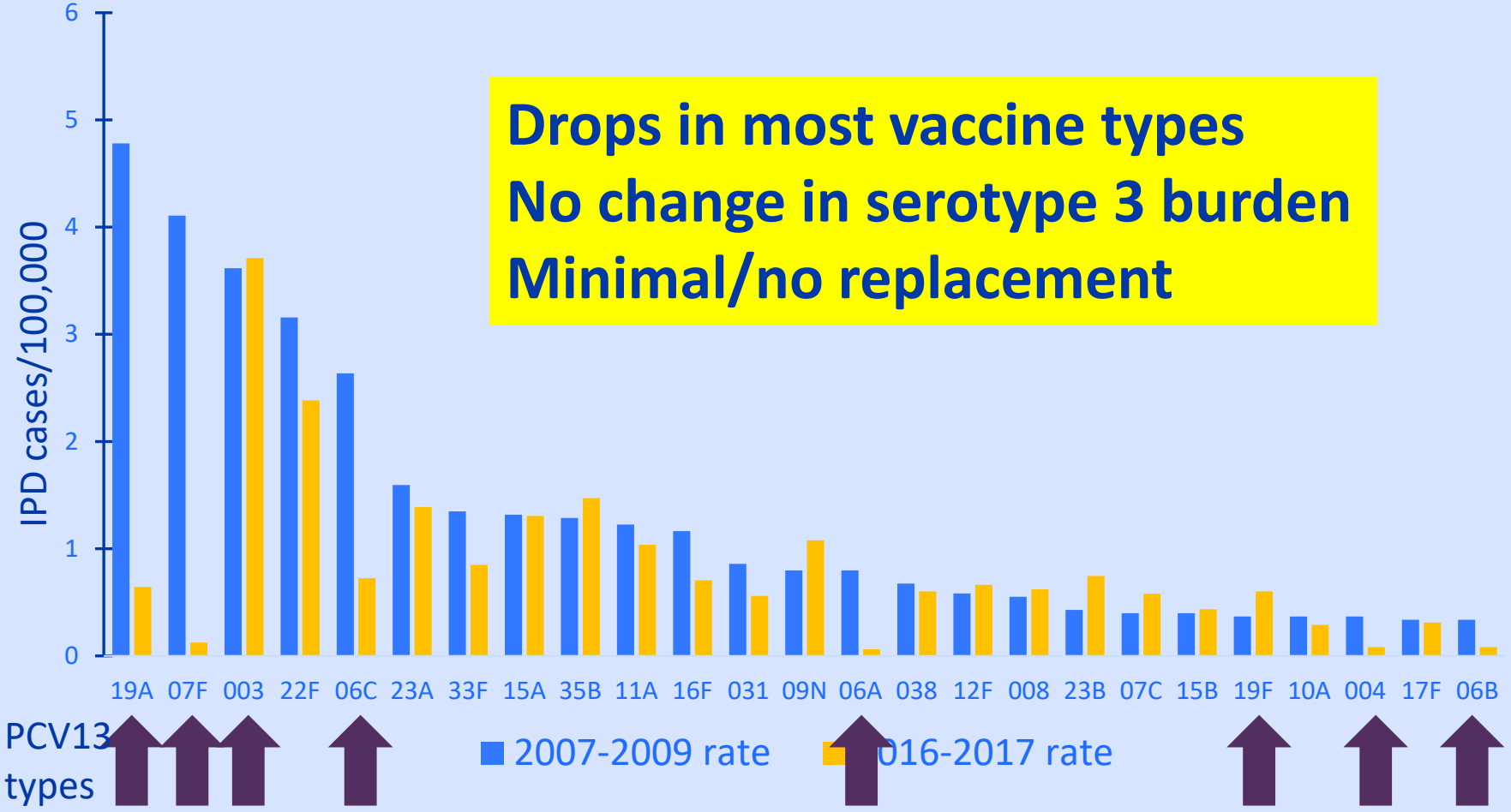

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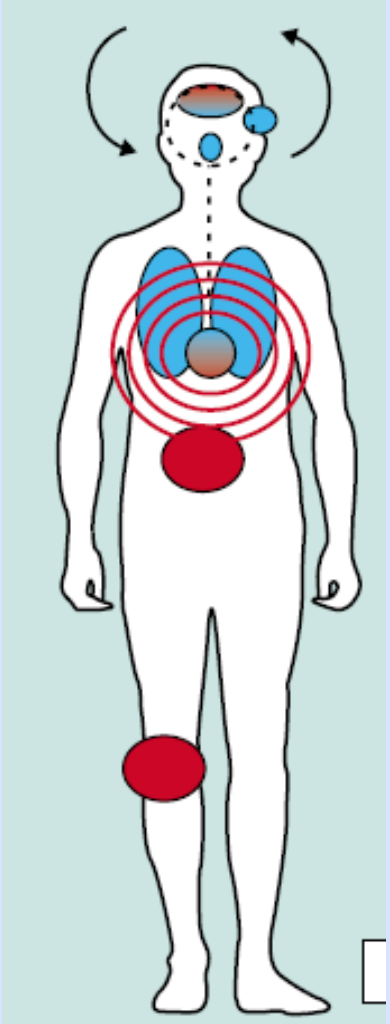
Evidence for ACIP's assessment of Adult PCV13 policy: Invasive disease



- PCV13-type IPD incidence in US adults ≥65 years old declined 68% after pediatric PCV13 began in 2010; no change from 2014 to 2016
  - PCV13 serotype 3 most common serotype
  - Low PCV13 disease rates among Alaska Natives and Navajo before implementation of adult program (indirect effects); no change after
- Mathematical model estimated direct PCV13 effects on observed IPD trends in IPD among adults ≥65 years old
  - Between 80-760 IPD cases prevented since 2014 among U.S adults ≥65 years; benefits decreasing over time
- PCV13 effectiveness against PCV13-type IPD 47% (95%CI 4–71%) to 65% (95%CI 19–85%) in 2 case-control studies
  - Confidence intervals overlap with the CAPiTA PCV13

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

Pillishvili, ACIP meeting Feb 2018; Hammitt, ACIP June 2018

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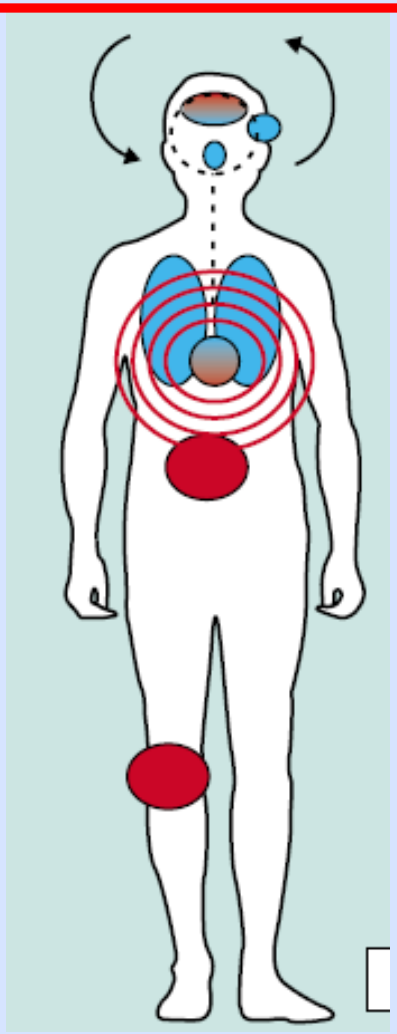

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- **PCV13 effective in older adults (serotype 3?)**
- **Direct benefit of adult program small in most recent years**

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

Pillishvili, ACIP meeting Feb 2018; Hammitt, ACIP June 2018

Evidence for ACIP's assessment of Adult PCV13 policy: Pneumonia

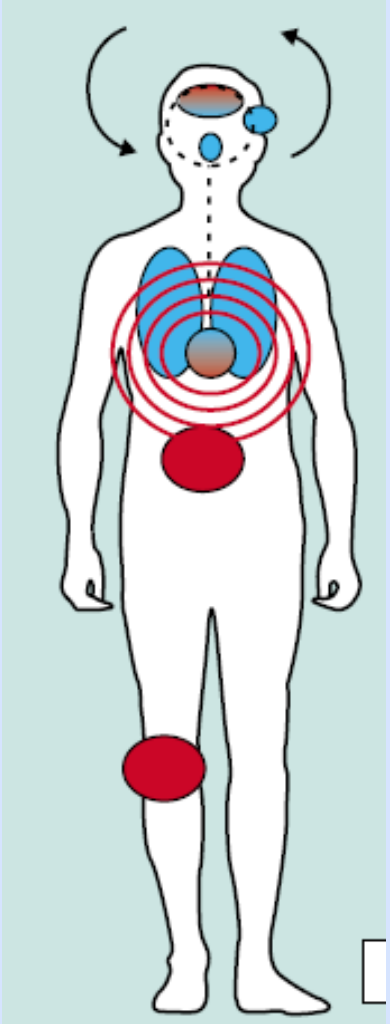


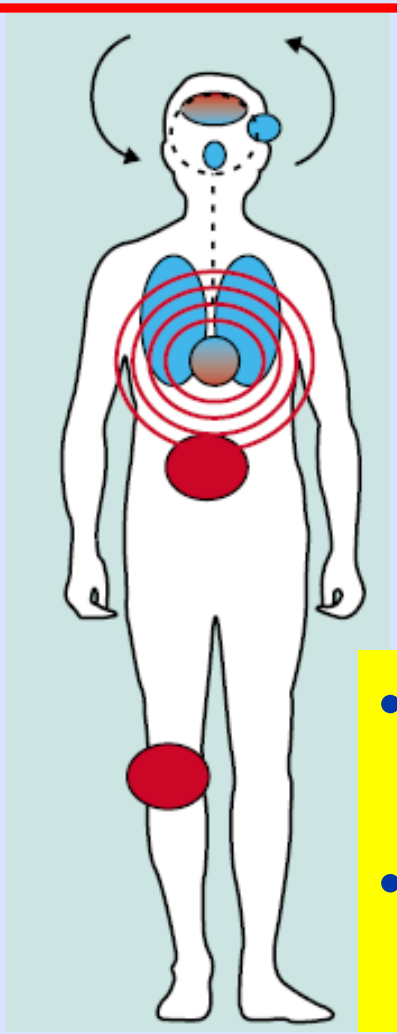
Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

- PCV13 effectiveness against PCV13-type **pneumonia** 73% (95% CI 13–92) demonstrated in a test negative case-control study design
  - Confidence intervals overlap with CAPiTA PCV13 efficacy estimates of 45% (95%CI 14–65%) against PCV13-type pneumonia

- Among American Indians in the southwest US, 26% of chest x-ray confirmed pneumonia had pneumococcal diagnosis; of these, 31% PCV13-types by SSUAD, mostly serotype 3

McLaughlin, ACIP Feb 2018; Hammitt, ACIP June 2019

Evidence for ACIP's assessment of Adult PCV13 policy: Pneumonia



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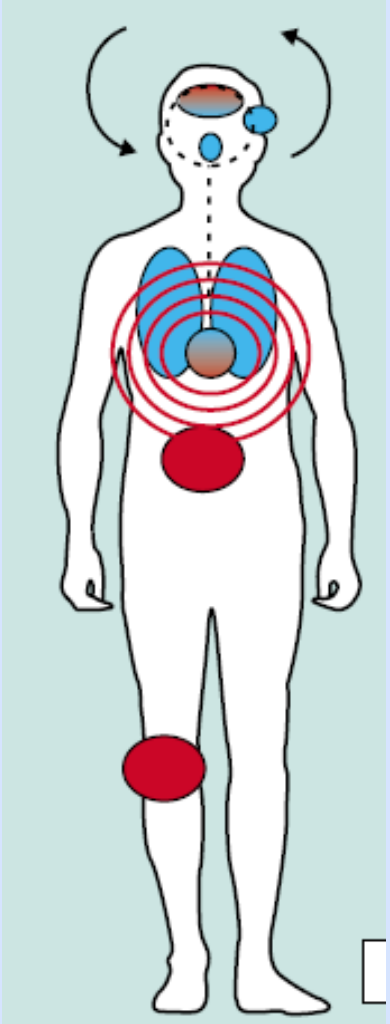
- **PCV13 effective against pneumonia (serotype 3?)**
- **Remaining pneumonia mostly nonvaccine types or serotype 3**

McLaughlin, ACIP Feb 2018; Hammitt, ACIP June 2019

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

Evidence for ACIP's assessment of Adult PCV13 policy: Nasopharyngeal Carriage



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- Nasopharyngeal carriage before and after PCV13 introduction in adults ≥65 in Atlanta
  - Children <5 years:
    - PCV13-serotype carriage declined from 8% in 2011 to <1% in 2017
    - Total *S. pneumoniae* carriage remained the same (~30%)
  - Adults ≥65 years:
    - PCV13-serotype carriage 0.2% in 2015-16
    - Total *S. pneumoniae* carriage also low (1.8%)

Thomas, ACIP meeting Oct 2017; Lessa, ACIP meeting Oct 2017

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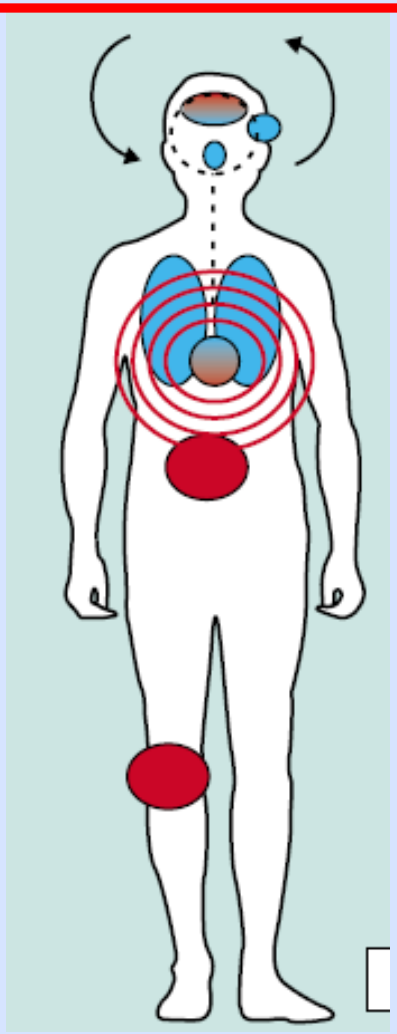

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Older adults rarely exposed to PCV13 serotypes

ACIP Meetings coming soon

- October 2018: Discussion and data review
  - PCV13 impact on IPD and serotype distribution for the remaining disease burden
  - U.S. trends in US pneumonia hospitalizations, noninvasive pneumococcal pneumonia in ABCs sites for older adults
  - Cost effectiveness of PCV13 for adults ≥65 year old
  - Preliminary EtR and GRADE

- February 2019: Tentative vote
  - Should PCV13 be administered routinely to all adults aged ≥65 years in a setting of sustained PCV13 indirect effects?

ACIP Evidence to Recommendation (EtR)

Goal: develop a uniform approach to evaluation and use of the evidence base for ACIP recommendations

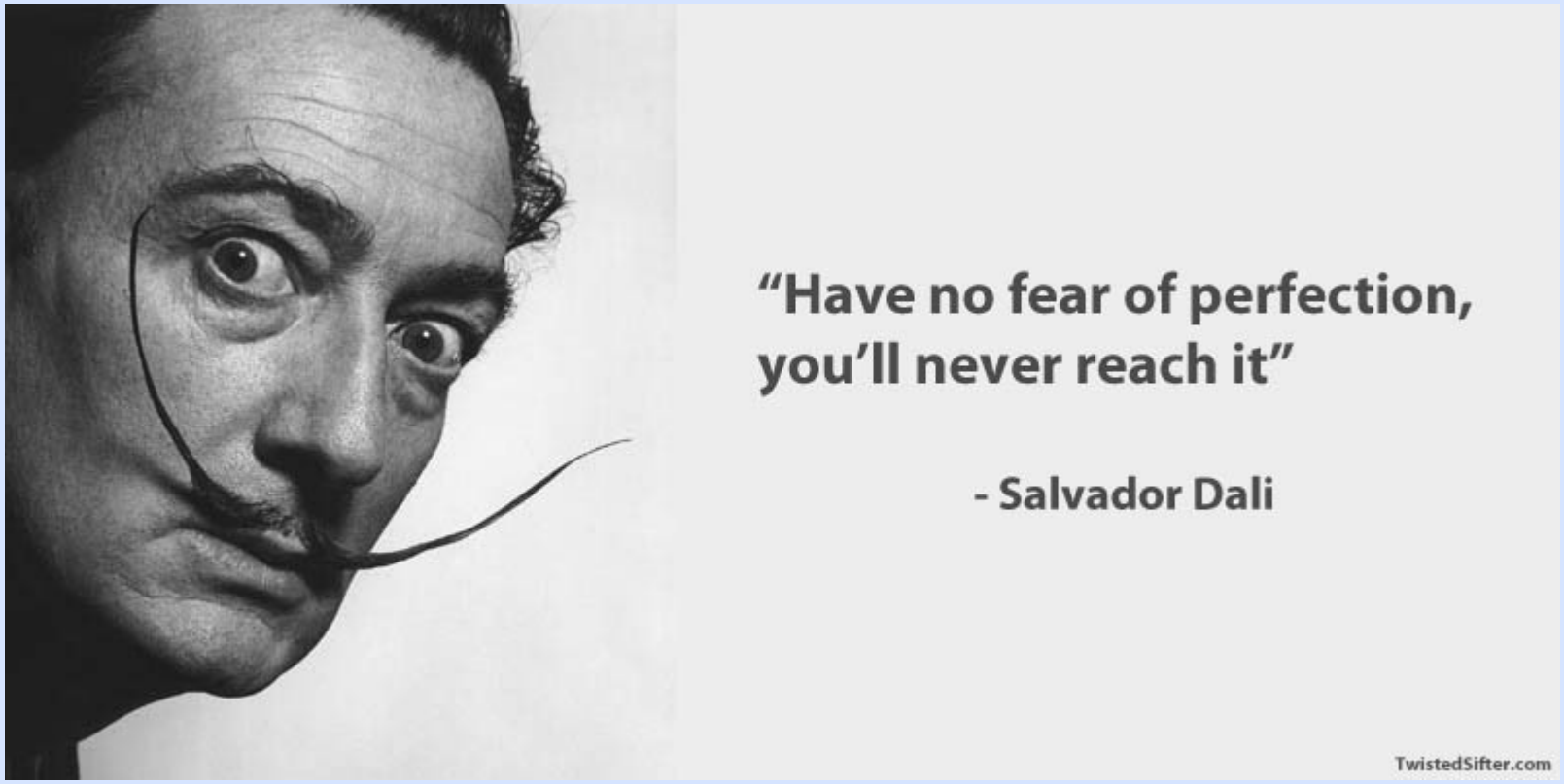
Framework:

- Statement of problem
  - Public health priority
  - Burden of disease
- Benefits and harms (GRADE)
  - Balance of desirable and undesirable effects
  - Certainty in evidence
  - Values and preferences of target population
- Acceptability to stakeholders
- Resource use
  - Health economic analyses
- Feasibility
  - Implementation considerations

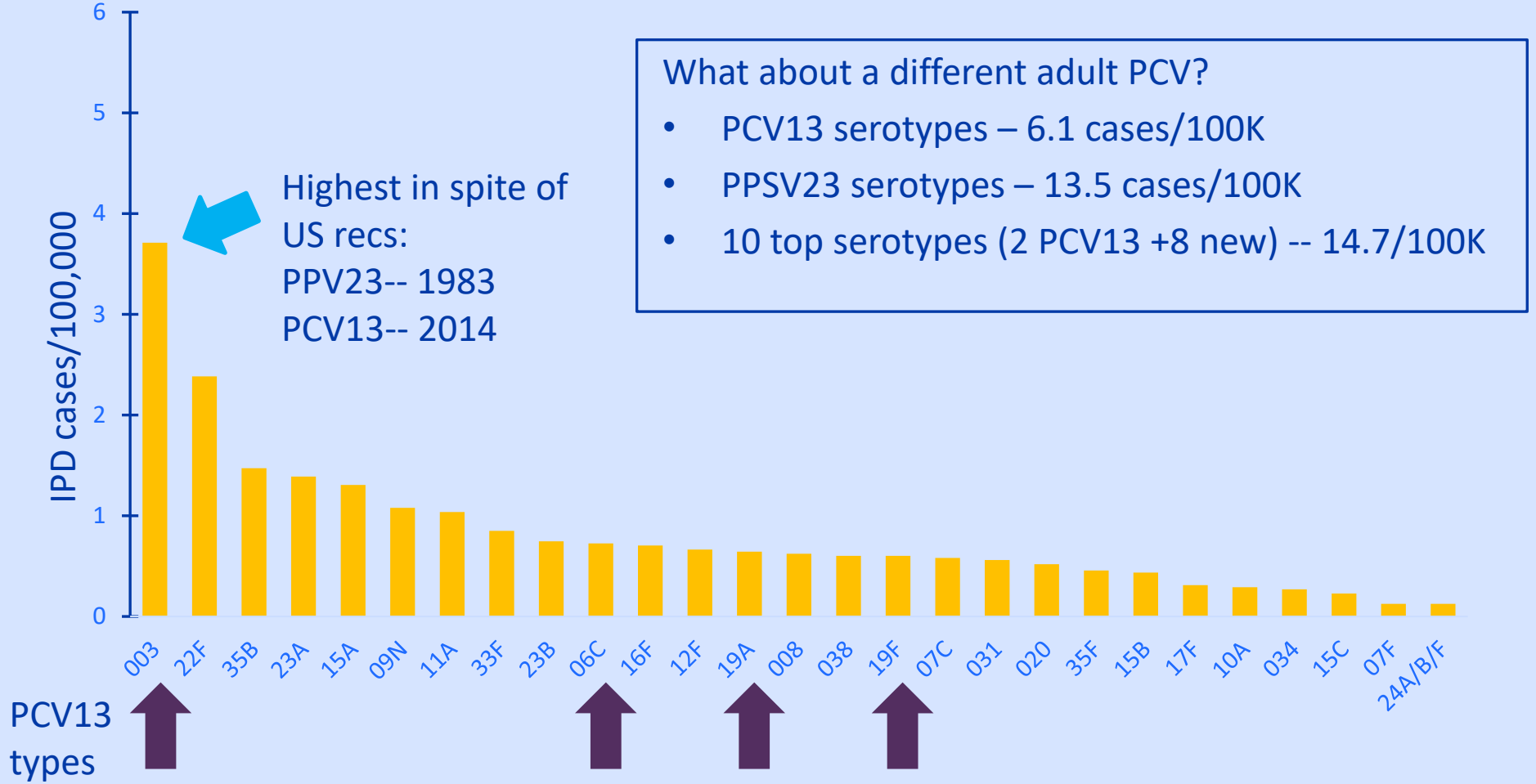
ACIP PCV13 recommendations for adults: To drop or not to drop?

- DROP PCV13 FOR OLDER ADULTS
  - Disease caused by vaccine types now uncommon, except serotype 3
  - Preliminary evidence suggests herd effects from children drive low rates in adults, not direct effects
  - Vaccination is a lot of time and expense for low likelihood of benefit
- DON'T DROP
  - Vaccine is safe and effective
  - Communication/acceptability challenges, i.e. "Drop the more effective vaccine?"
  - Logistics/systems challenges: If new vaccines around the corner, why not wait to change and avoid rapid program shifts?

What serotypes would we include in the ideal adult pneumococcal conjugate vaccine?



Top serotypes causing IPD in US adults 65+ years, 2016/17

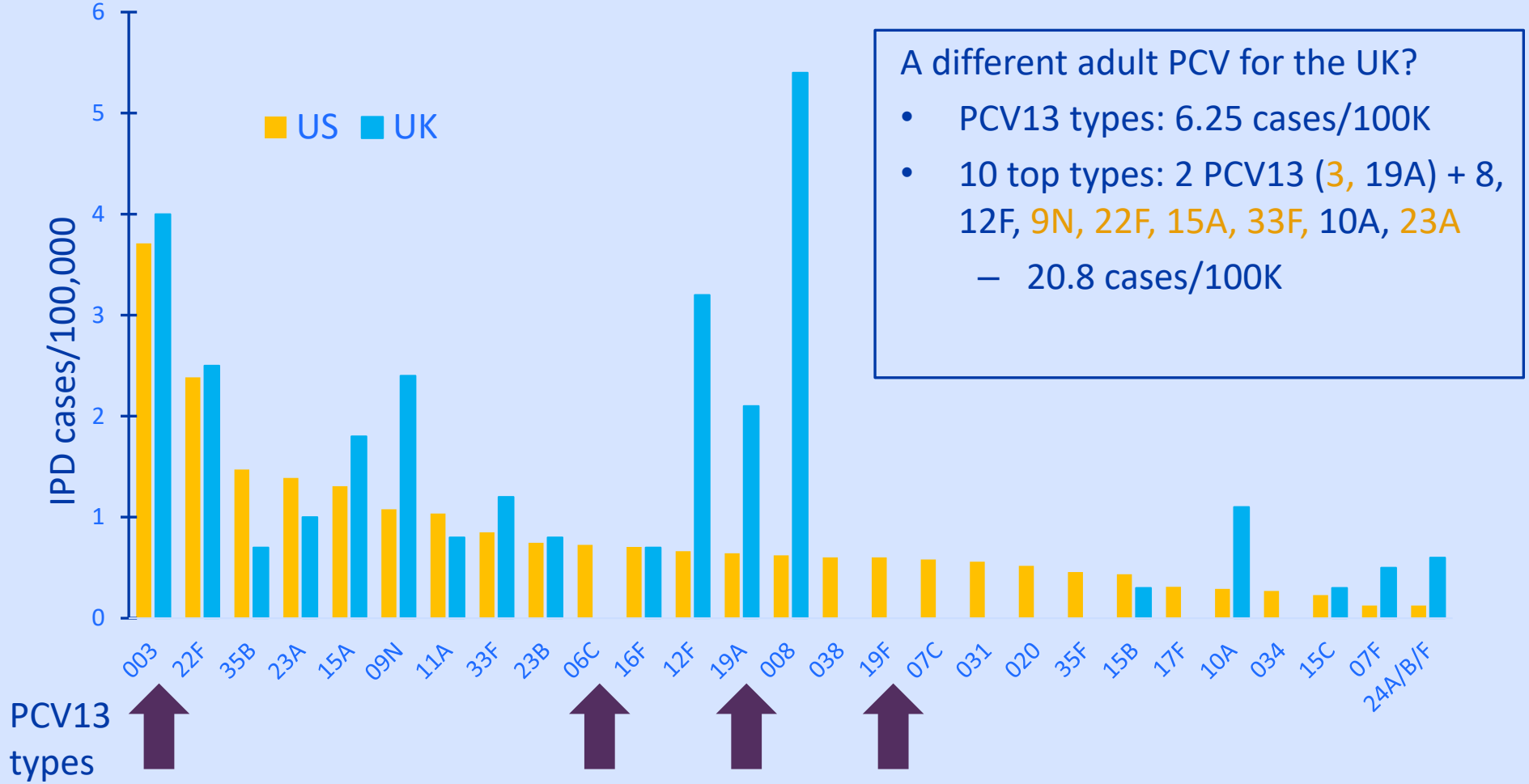


What about a different adult PCV?

- PCV13 serotypes – 6.1 cases/100K
- PPSV23 serotypes – 13.5 cases/100K
- 10 top serotypes (2 PCV13 +8 new) -- 14.7/100K

Source: US Centers for Disease Control and Prevention, Active Bacterial Core surveillance

Top serotypes causing IPD in US and UK adults 65+ years, 2016/17



A different adult PCV for the UK?

- PCV13 types: 6.25 cases/100K
- 10 top types: 2 PCV13 (3, 19A) + 8, 12F, 9N, 22F, 15A, 33F, 10A, 23A
  - 20.8 cases/100K

Sources: US CDC Active Bacterial Core surveillance; Ladhani et al Lancet Infect Dis 2018

Considerations for designing an adult vaccine

- Serotype 3 remains common, even with recs for PCV13 (U.S.) and PPV23; differs from other PCV antigens. Is a better serotype 3 component possible?
- In push to cover more serotypes, potentially to replace PPSV23, will individual components interfere with each other's ability to elicit an immune response?
- Given herd effects, should adult vaccines target different serotypes than those in the pediatric formulation? Or would production/licensing issues preclude this option?
- Will costs permit use in low- and middle-income countries?
- How to chose best serotypes to include, given differences between countries? 8-10 antigens likely to target substantial burden

Questions

What should ACIP do about the adult recommendation?

What/how many serotypes should an adult vaccine have?

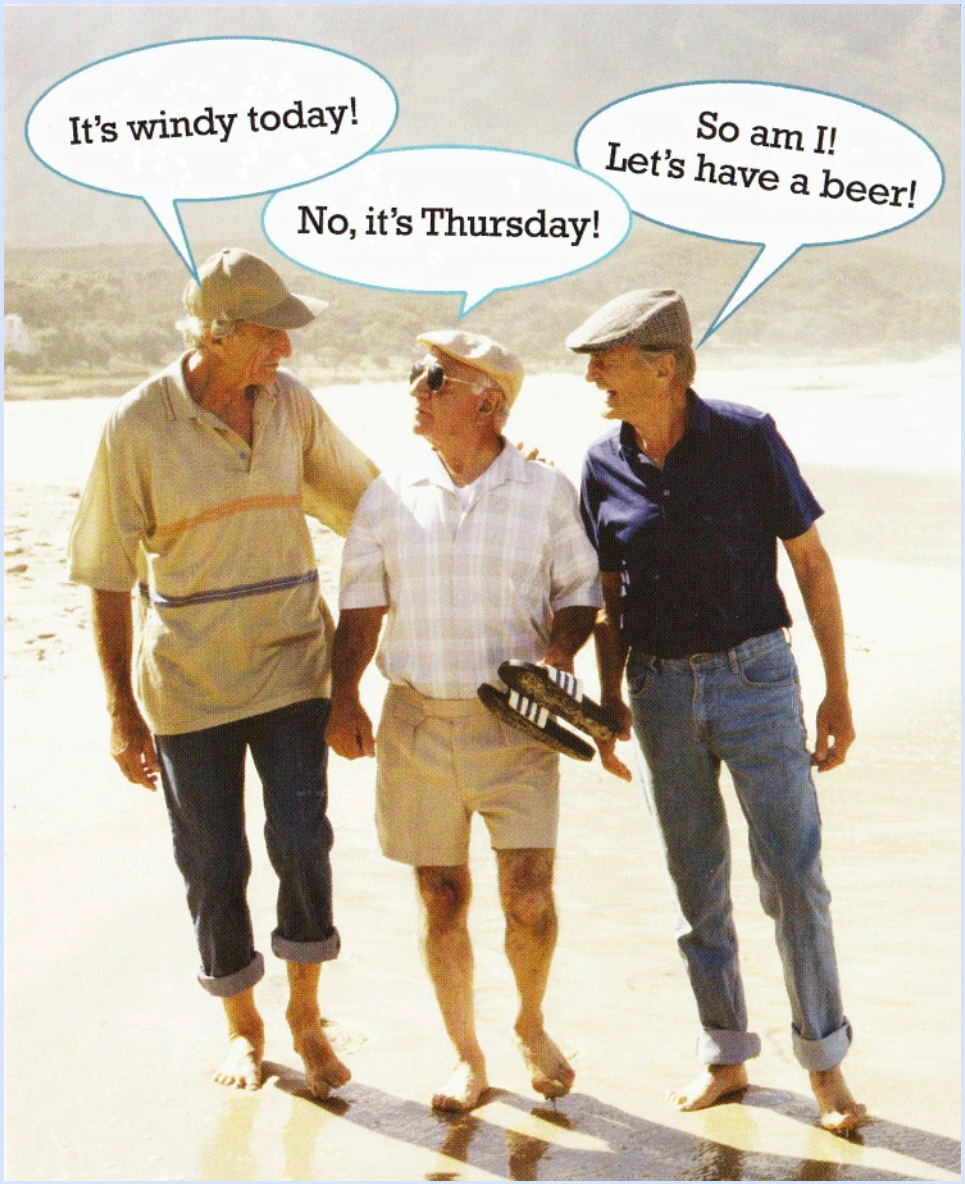


Photo source: nowthatsnifty.blogspot.com